Relaxation rate of the respiratory muscles and prediction of extubation outcome in prematurely born infants

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Short title: Prediction of extubation by respiratory muscle relaxation

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ABSTRACT

Background: Accurate prediction of extubation outcome could result in a significant reduction of respiratory morbidity in premature neonates.

Objectives: To assess whether the respiratory muscle time constant of relaxation ($\boldsymbol{\tau}$) predicted extubation outcome in mechanically ventilated, premature infants.

Methods: Forty-six mechanically ventilated infants with a median gestational age of 26 [interquartile range (IQR) 25-29] weeks were prospectively studied. $\boldsymbol{\tau}$ was calculated from the reciprocal of the slope of the airway pressure decline as a function of time. Measurements of $\boldsymbol{\tau}$ were done during five to ten minutes of a spontaneous breathing test (SBT) prior to extubation. During the first and last minute of the SBT, $\boldsymbol{\tau}_1$ and $\boldsymbol{\tau}_2$ respectively were assessed and the difference between them was calculated ($\boldsymbol{\Delta\tau}$).

Results: The median $\boldsymbol{\tau}_2$ was significantly higher in infants that failed extubation [20.7(IQR 12.9-34.7)sec/cmH_2O] compared to infants that succeeded extubation [8.2(IQR 6.2-17.8) sec/cmH_2O, p=0.002]. The median $\boldsymbol{\Delta\tau}$ was significantly higher in infants that failed extubation [10.3(IQR 4.4-23.9)sec/cmH_2O] compared to infants that succeeded extubation [-1.63(IQR -5.7-0.3)sec/cmH2O, p=0.001]. Extubation failure was associated with $\boldsymbol{\tau}_2$ (p=0.011) and $\boldsymbol{\Delta\tau}$ (p=0.010) after correcting for postmenstrual age, patent ductus arteriosus and intraventricular haemorrhage. Receiver operator characteristic curve analysis demonstrated that $\boldsymbol{\Delta\tau}$ predicted extubation failure with an area under the curve of 0.937. A $\boldsymbol{\Delta\tau}$ of +1.02 sec/cmH_2O predicted extubation failure with 94% sensitivity and 83% specificity.

Conclusions: The respiratory muscle time constant of relaxation during a SBT was significantly greater in infants who failed extubation and could be used to predict extubation outcome in prematurely born infants.

INTRODUCTION

Mechanical ventilation (MV) is a lifesaving intervention for prematurely born infants. Prolonged MV, however, is associated with significant respiratory morbidity [1], but inappropriately early discontinuation of MV (extubation) might precipitate a sudden deterioration with adverse consequences and necessitate re-institution of MV (reintubation) [2]. Various factors have been evaluated in order to predict extubation outcome such as blood gases [3], minute ventilation [4, 5], lung volume and compliance measurements [5-7], assessment of cardiorespiratory variability [8, 9] and composite indices describing respiratory muscle efficiency [2, 3, 10]. Unfortunately, accurate prediction of extubation outcome remains evasive as the evaluated indices have been shown to demonstrate high sensitivity, but only moderate specificity.

The ability to sustain the work of breathing is dependent on the functional capacity of the respiratory muscles to cope with the imposed workload [11]. Previous studies investigating respiratory muscle function in prematurely born infants have shown that univariate indices such as the maximal inspiratory or expiratory pressures have not been useful, as differences according to extubation outcome were not statistically significant when the results were related to birth weight [12]. Furthermore, composite indices of respiratory muscle function such as the tension-time index of the respiratory muscles did not perform significantly better in predicting extubation outcome than gestational age or birth weight [10].

The functional state of the respiratory muscles and the risk for muscle fatigue can be assessed by measuring the rate of relaxation of the respiratory muscles [13]. The rate of decline in airway pressure during a spontaneous breathing test when an infant is switched from MV to endotracheal continuous positive airway pressure (CPAP) can be used as a surrogate for the measurement of the rate of relaxation. Healthy skeletal muscles relax rapidly, but when skeletal muscles operate against an increased load, their rate of contraction and relaxation slows [14]. The rate of relaxation can be quantified by the time constant of respiratory muscle relaxation – $\boldsymbol{\tau}$ (tau) which is calculated as the reciprocal of the absolute value of the slope of the pressure decline as a function of time at the lower 60% part of the curve. Higher values of $\boldsymbol{\tau}$ indicate slower relaxation and increased risk for respiratory muscle fatigue, while lower values of $\boldsymbol{\tau}$ indicate rapid relaxation and healthy muscle function [15]. $\boldsymbol{\tau}$ has not been studied in prematurely born infants undergoing MV.

We hypothesized that $\boldsymbol{\tau}$ will be increased in premature infants who fail extubation. The aim of this study was to test that hypothesis and determine whether $\boldsymbol{\tau}$ predicted extubation outcome in mechanically ventilated premature infants.

MATERIALS AND METHODS

Subjects

Infants born at less than 34 completed weeks of gestation without congenital anomalies ventilated at King's College Hospital NHS Foundation Trust were eligible for study. The infants were ventilated with a Cole's shouldered endotracheal tube (size 2.5 or 3.0) on volume-targeted or pressure-controlled time-cycled ventilation with the SLE5000 neonatal ventilator or the SLE2000 infant ventilator (SLE, Croydon, UK). The study was approved by the London – Surrey Borders Research Ethics Committee (REC Reference 15/LO/2111). Written, informed parental consent was obtained.

The infants were studied when they were clinically stable and ready for extubation. Extubation was considered, as per unit policy, if the fraction of inspired oxygen (FiO_2) was less than 0.4, the infant had acceptable blood gases, that is a pH > 7.25 and a $PaCO_2$ < 8.5

kPa, and their breathing rate was above the set ventilator rate. Sedation was discontinued at least 12 hours before extubation and all infants were receiving caffeine at a standard maintenance dose.

Study protocol

When the clinical team decided that an infant was ready for extubation, the infant underwent a SBT which consisted of switching the infant from MV to endotracheal (ET)-CPAP for a period of 5 to 10 minutes during which time the oxygen saturation (SpO_2) and heart rate were monitored [16]. During the SBT, the ET-CPAP level was the same pressure as the positive end expiratory pressure during mechanical ventilation. A failed SBT was recorded if the infant had either a bradycardia with a heart rate of less than 100 per minute for more than 15 seconds and/or a fall in SpO_2 below 85% despite a 15% increase in the fraction of inspired oxygen (FiO_2). The study was then stopped and MV resumed. The clinical team caring for the infant was not present during the SBT and not made aware of the results. Regardless of the result of the SBT, all infants were extubated. Infants were extubated on to either heated, humidified, high-flow nasal cannula or nasal CPAP at the discretion of the clinical team. Reintubation within 72 hours of extubation was the primary outcome of the study [16]. The indications for reintubation were development of respiratory acidosis ($pH<7.25$ and $PaCO_2$ >8.5 kPa), a significant apnoea requiring bag and mask ventilation or frequent episodes of apnoea requiring stimulation or a $FiO_2>0.6$ to maintain an oxygen saturation in the range of 90–95% [16].

Monitoring equipment

A respiratory function monitor (NM3 respiratory profile monitor (RPM) (Philips Respironics, Connecticut, USA [17, 18] was used. The monitor was connected to a Laptop (Dell Latitude, Dell, Bracknell, UK) with customised Spectra software (3.0.1.4) (Grove Medical, London, UK). The NM3 RPM had a combined pressure and flow sensor which was placed between the endotracheal tube and the ventilator circuit. Flow was measured using a fixed orifice pneumotachograph. One of the tubes from the pneumotachograph was connected to a pressure transducer which measured airway pressure.

Calculation of the time constant of relaxation

The time constant of respiratory muscle relaxation ***(τ)*** was calculated as the reciprocal of the absolute value of the slope of the pressure decline as a function of time at the lower 60% of the curve (figure 1) [15]. The part of the trace with a smooth pressure decay was hand selected and analysed. Breaths whose waveforms exhibited evidence of expiratory diaphragmatic braking were excluded from the analysis. For each subject, the mean $\boldsymbol{\tau}$ value of at least five consistent breaths was recorded. $\boldsymbol{\tau}$ was calculated during the first minute ($\boldsymbol{\tau}_1$) and the last minute of the SBT ($\boldsymbol{\tau}_2$). The difference between these values ($\boldsymbol{\tau}_2 - \boldsymbol{\tau}_1$) was calculated ($\boldsymbol{\Delta\tau}$) (delta tau).

Information from the medical records

Gender, gestation age at birth, birth weight, postmenstrual age, postnatal age and weight at the time of SBT were recorded. The FiO_2, mean airway pressure and backup rate during MV and the arterial pressure of CO_2 (P_aCO_2) and pH within two hours prior to the SBT were also recorded. The inspiratory pressures that were spontaneously generated during the SBT and the PEEP during the SBT were recorded from a mean of ten spontaneous breaths during the last minute of the SBT. Endotracheal tube leak was estimated as the difference of inspiratory minus expiratory tidal volume, expressed as a percentage of the inspiratory tidal volume.

Information recorded from the infant's medical notes included whether the infant had a patent ductus arteriosus (PDA), had been exposed to antenatal steroids or had had an intraventricular haemorrhage (IVH). A PDA was diagnosed clinically and confirmed by echocardiography. Administration of antenatal corticosteroids was recorded as a positive if at least two doses were given. The cranial ultrasound was recorded as normal if there was no intraventricular haemorrhage or intracranial pathology.

Sample size calculation

The sample size calculation was based on the assumption that a difference in $\boldsymbol{\tau}$ of 26 between infants that failed and infants that succeeded extubation was clinically significant based on values of $\boldsymbol{\tau}$ that were observed before and after induced diaphragmatic fatigue in healthy young men [19]. The standard deviation of $\boldsymbol{\tau}$ was obtained from pilot data and was equal to 22. The required sample size to detect an increase in $\boldsymbol{\tau}$ of 26 with 90% power at the 5% level of statistical significance was 15 subjects in each group.

Statistical analysis

Data were tested for normality with the Kolmogorov–Smirnoff test and found not to be normally distributed. Hence, differences between those who did and did not fail extubation were assessed for statistical significance using the Mann-Whitney rank sum test or Chi-squared test, as appropriate. The factors that were statistically different (p value <0.05) were inserted into a multivariate logistic regression model with extubation failure as the outcome. Variables without normal distribution were logarithmically transformed. Multi-collinearity among the independent variables in the regression analysis was assessed by calculation of the tolerance for the independent variables.

The performance of the factors that were identified from the multivariate regression model in predicting extubation failure was assessed by receiver operator characteristic (ROC) curve analysis and estimation of the corresponding area under the curve (AUC). The relationship of the duration of the SBT with $\boldsymbol{\tau}$ was assessed with the Spearman-rho correlation coefficient (r). Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago IL).

RESULTS

Between 1 February 2016 and 1 August 2016, 113 infants were ventilated on the Neonatal Unit. Sixty-seven infants were excluded from the study as they had congenital anomalies, they were born at more than 34 weeks of gestational age or were extubated before the SBT could be performed. Forty-six infants underwent the SBT. Five infants failed the SBT and all of them failed extubation. Forty-one infants passed the SBT, twenty three were subsequently successfully extubated and eighteen failed extubation. $\boldsymbol{\tau}$ was not assessed in the infants that failed the SBT, as they had apnoeas and hence there was no airway pressure waveform for analysis. The infants that failed extubation had significantly lower postmenstrual age and weight at the time of the SBT and significantly higher $\boldsymbol{\tau}_2$ and $\boldsymbol{\Delta\tau}$ compared to the premature infants that succeeded extubation (Table 1). Premature infants that failed extubation had a significantly higher incidence of abnormal cranial ultrasound examinations and PDA (Table 1). Multivariate regression analysis revealed that $\boldsymbol{\tau}_2$ and $\boldsymbol{\Delta\tau}$ were significantly related to extubation failure independently of PMA, PDA and cranial ultrasound abnormalities (Table 2). Weight was excluded from the multivariate regression model because of collinearity with postmenstrual age. The median (IQR) respiratory rate during the first minute of the SBT was 67 (59 - 78) and during the last minute of the SBT was 72 (60 - 87), p=0.292. ROC curve analysis demonstrated in predicting extubation success PMA had an AUC of 0.688, $\boldsymbol{\tau}_2$ an AUC of 0.790 (figure 2a) and $\boldsymbol{\Delta\tau}$ an AUC of 0.937 (figure 2b). A $\boldsymbol{\Delta\tau}$ equal to +1.02 sec/cm H_2O predicted extubation failure with 94% sensitivity and 83% specificity.

The duration of the SBT was not significantly related to $\boldsymbol{\tau}_2$ (r=0.044, p=0.733) or $\boldsymbol{\Delta\tau}$ (r=0.021, p=0.869).

DISCUSSION

We have demonstrated that prematurely born infants who failed extubation exhibited significantly slower respiratory muscle relaxation compared to those who were successfully extubated. In addition, we have highlighted that the change in $\boldsymbol{\tau}$ during a spontaneous breathing test had a high sensitivity and specificity in predicting extubation failure. The SBT has been reported to have a sensitivity of 97% in predicting extubation outcome [16], which is enhanced to 100% by incorporating measurements of respiratory variability [8]. Unfortunately, the specificity of the SBT is only moderate (73%) [3] which increases only to

75% by incorporating respiratory variability information [18]. In our cohort, the SBT had a sensitivity of 100% in predicting extubation failure, but the specificity of the test was low (22 %).

Previous studies have evaluated the relaxation rate as an index of respiratory muscle fatigue in healthy adults [14, 19, 20]. Goldstone et al [21] reported that the relaxation rate in intubated adults being weaned from mechanical ventilation was slower in patients that failed to wean from MV. Furthermore, they also reported that measurements from the endotracheal tube, as used in this study, reflected the relaxation of the diaphragm as assessed by oesophageal and transdiaphragmatic catheters [21].

The importance of our study is that it is the first neonatal study to report that the relaxation rate of the respiratory muscles can be used to accurately predict extubation outcome in premature infants. Our study also highlights a potential pathophysiological mechanism that might be implicated in respiratory failure in prematurely born infants. While it is known that prematurely born infants generate lower inspiratory pressures [22], we now describe that they also exhibit a relaxation pattern that might put them at a higher risk of muscle fatigue. A number of anatomical features render the infantile respiratory muscles more prone to dysfunction. Unlike the adult dome-shaped diaphragm, the newborn diaphragm is morphologically flattened and inserted to the chest wall with a larger angle, resulting in smaller zone of apposition and decreased range of displacement [23]. Structurally, the newborn diaphragm consists of fewer fatigue-resistant slow twitch fibres, decreased oxidative capacity and a low total cross sectional area of all fibre types [24]. Furthermore, the premature infants in our cohort had been ventilated for long periods (interquartile range 3-32 days) and prolonged mechanical ventilation can lead to ventilator-induced diaphragmatic dysfunction [25]. Even brief mechanical ventilation has been shown to result in diaphragm atrophy and contractile dysfunction as a result of oxidation, diaphragmatic proteolysis and reduced protein synthesis [25].

Interestingly, the infants that were successfully extubated had a lower median τ at the end of the SBT compared to the median τ at the beginning of the SBT (negative $\Delta\tau$). This might represent the functional sufficiency of the respiratory muscles to undertake the work of breathing as they transition to lower levels of support

Theoretically, as the duration of the SBT in our study ranged from 5 to 10 minutes, the duration of the test could have influenced our results. The infants who underwent a longer test might have had a longer period for muscle fatigue to be induced by breathing against the resistance of the endotracheal tube. The duration of the test, however, was not related to $\boldsymbol{\tau}$ in our cohort. In our study we report a median endotracheal tube leak of 6-7%. It is standard practice in our unit to use shouldered endotracheal tubes which are associated with a low level of leak (26). Further studies in units that routinely use straight tubes could elucidate whether higher leaks might render the relaxation pattern unsuitable as a predictor of extubation outcome.

The strengths of our study include that the clinical team was not informed of the SBT result and hence were not biased with regard to the time of extubation. By measuring the rate of relaxation in intubated subjects we bypassed the upper airway and the possible contribution of upper airway dysfunction in extubation failure. Our study has some potential limitations. Measuring the rate of relaxation through the endotracheal tube in a ventilated subject might theoretically not accurately reflect respiratory muscle function as the measurements might be skewed by the resistance of the ventilator circuit and of the upper and lower airways. Increased resistance of the airways or the endotracheal tube would impose an additional workload on the respiratory muscles and slow their relaxation, especially in the face of impeding muscle fatigue [13]. To overcome that problem, we measured the difference in $\boldsymbol{\tau}$ when there were no changes in the level of respiratory support or use of anendotracheal tube during the SBT, hence the difference could be selectively attributed to respiratory muscle changes. We did not measure the relaxation time in infants who failed the SBT, but a failed SBT is already known to be highly predictive of extubation failure [16]. Our results highlight that a successful SBT can only accurately predict extubation failure when the rate of relaxation is taken into account. We also acknowledge that the airway pressure waveform has not been proven to reflect diaphragmatic activity in ventilated prematurely born newborns. It is plausible that these infants might have active expiration via activation of the abdominal muscles as accessory respiratory muscles, thus we have called our index “rate of relaxation of the respiratory muscles” rather than “diaphragmatic rate of relaxation”.

Our results have an obvious potential application. Modern neonatal ventilators incorporate a proximal pressure sensor and display the relevant pressure-time waveforms. Thus, the information on the rate of relaxation can be processed in real time by a customised ventilator software and inform the clinician as to the likelihood of extubation success.

In conclusion, we have demonstrated that the respiratory muscle time constant of relaxation is significantly higher in premature infants that fail extubation compared to premature infants that succeed extubation. We highlight that $\boldsymbol{\Delta\tau}$ can be used to predict extubation outcome in premature infants with high sensitivity and specificity.

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Contributors' statement:

TD conceived the study, participated in the analysis of the data and drafted the first version of the article. OK collected the data and participated in the analysis of the data. AG supervised the project, contributed to the study design and interpretation of the results and critically revised the manuscript. All authors were involved in the preparation of the manuscript and approved the final manuscript as submitted.

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FIGURE LEGENDS

Figure 1: Patterns of respiratory muscle relaxation: slower rate of relaxation and increasing values of $\boldsymbol{\tau}$ describe increasing respiratory muscle dysfunction and risk for muscle fatigue.

Figure 2: ROC curves for $\boldsymbol{\tau}$2 (a) and delta $\boldsymbol{\Delta\tau}$ (b) to predict extubation failure.

Table 1: Demographics and mechanical ventilation settings at the start of the SBT and inspiratory muscle time constant of relaxation according to successful and failed extubation

Data are presented as median (IQR) or n (%)

	Successful Extubation	Failed Extubation	
	N=23	*N*=18	p-value
GA (weeks)	28 (25 – 30)	26 (25 – 27)	0.208
PMA (weeks)	31 (29 - 33)	27 (26 - 32)	0.037
BW (kg)	0.88 (0.70 – 1.36)	0.88 (0.77 - 0.95)	0.368
Male gender	12 (52)	8 (44)	0.792
Weight (kg)	1.36 (1.06 – 1.69)	1.00 (0.83 - 1.21)	0.023
Postnatal age (days)	16 (2 – 47)	9 (4 - 43)	0.731
Antenatal Steroids	19 (82)	11 (61)	0.540
Abnormal Cranial US	3 (13)	7 (39)	0.047
Patent Ductus Arteriosus	2 (9)	6 (33)	0.025
ETT size 2.5 mm	4 (17)	4 (22)	0.538
ETT Leak (%)	6 (2 - 13)	7 (4 - 14)	0.494
No surfactant	1 (4)	0 (0)	0.152
FiO_2	0.27 (0.22 – 0.37)	0.26 (0.22 - 0.31)	0.939
MAP (cm H_2O)	8 (7 – 9)	8 (7 - 9)	0.627
RR_1	71 (56 – 89)	76 (63 – 81)	0.486
RR_2	67 (59 – 79)	68 (60 -78)	0.674
Delta RR	-8 (-14 – 12)	-5 (-8 – 1)	0.511
Ti_1 (sec)	0.41 (0.31 – 0.45)	0.32 (0.31 – 0.37)	0.069
Ti_2 (sec)	0.37 (0.29 – 0.46)	0.36 (0.31 – 0.44)	0.674

Delta Ti	0.01 (-0.06 – 0.07)	0.01 (-0.01 – 0.06)	0.415
Backup rate	40 (40 – 45)	40 (30 - 40)	0.117
$PaCO_2$ (kPa)	6.26 (5.39 – 6.62)	6.89 (5.37 - 7.86)	0.162
pH	7.36 (7.33 – 7.40)	7.36 (7.32 -7.41)	0.937
Days of ventilation	8 (2 – 38)	9 (4 – 37)	0.838
PEEP (cm H_2O)	5.6 (4.2 – 6.3)	5.6 (4.8 – 6.0)	0.916
P_{insp} (cm H_2O)	7.0 (6.5 – 7.8)	6.8 (5.9 – 7.2)	0.236
Duration of SBT (min)	6 (5-8)	6 (5 – 8)	0.644
$\boldsymbol{\tau}_1$ (sec/cm H_2O)	11.3 (7.1 – 23.8)	10.7 (7.9 – 17.0)	0.608
$\boldsymbol{\tau}_2$ (sec/cm H_2O)	8.2 (6.2 – 17.8)	20.7 (12.9 – 34.7)	0.002
$\boldsymbol{\Delta\tau}$ (sec/cm H_2O)	-1.63 (-5.7 – 0.3)	10.3 (4.4 – 23.9)	0.001
Extubated to CPAP	11 (48)	7 (39)	0.752

SBT: spontaneous breathing trial, GA: gestational age, PMA: postmenstrual age, ETT: Endotracheal tube, BW: birth weight, FiO_2: fraction of inspired oxygen, MAP: mean airway pressure, RR_1: respiratory rate at during the first minute of the SBT, RR_2: respiratory rate during the last minute of the SBT, Delta RR= RR_2 – RR_1, Ti_1: inspiratory time during the first minute of the SBT, Ti_2: inspiratory time during the last minute of the SBT, Delta Ti=Ti_2 – Ti_1, $PaCO_2$: Arterial partial pressure of CO_2, P_{insp}: peak inspiratory pressure generated during spontaneous breathing, PEEP positive end expiratory pressure, $\boldsymbol{\tau}_1$: time constant of respiratory muscle relaxation during the first minute of the SBT, $\boldsymbol{\tau}_2$: time constant of respiratory muscle relaxation during the last minute of the SBT, $\boldsymbol{\Delta\tau} = \boldsymbol{\tau}_2 - \boldsymbol{\tau}_1$, CPAP: continuous positive airway pressure.

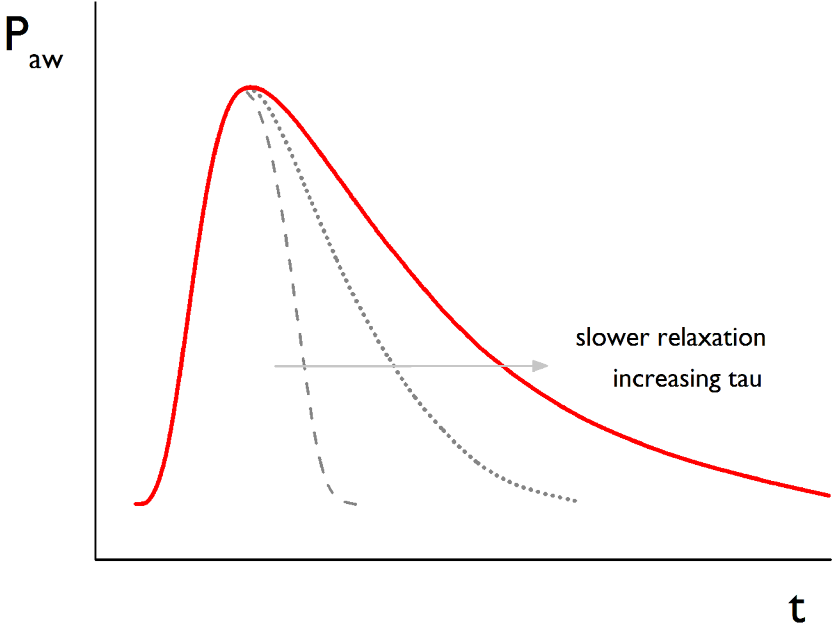
Table 2: Multivariate logistic regression analysis including τ_2 (a) or $\Delta\tau$ (b) for extubation outcome

a

	Odds Ratio	Confidence intervals	*P*-value
Postmenstrual age	1.097	0.841-1.429	0.495
Patent Ductus Arteriosus	0.259	0.025-2.737	0.262
Normal cranial ultrasound	6.924	0.905-52.955	0.062
τ_2	0.875	0.789-0.969	0.011

b

	Odds Ratio	Confidence intervals	*P*-value
Postmenstrual age	1.264	0.655-2.439	0.485
Patent Ductus Arteriosus	0.537	0.018-16.218	0.721
Normal cranial ultrasound	12.323	0.298-509.672	0.186
$\Delta\tau$	0.573	0.374-0.877	0.010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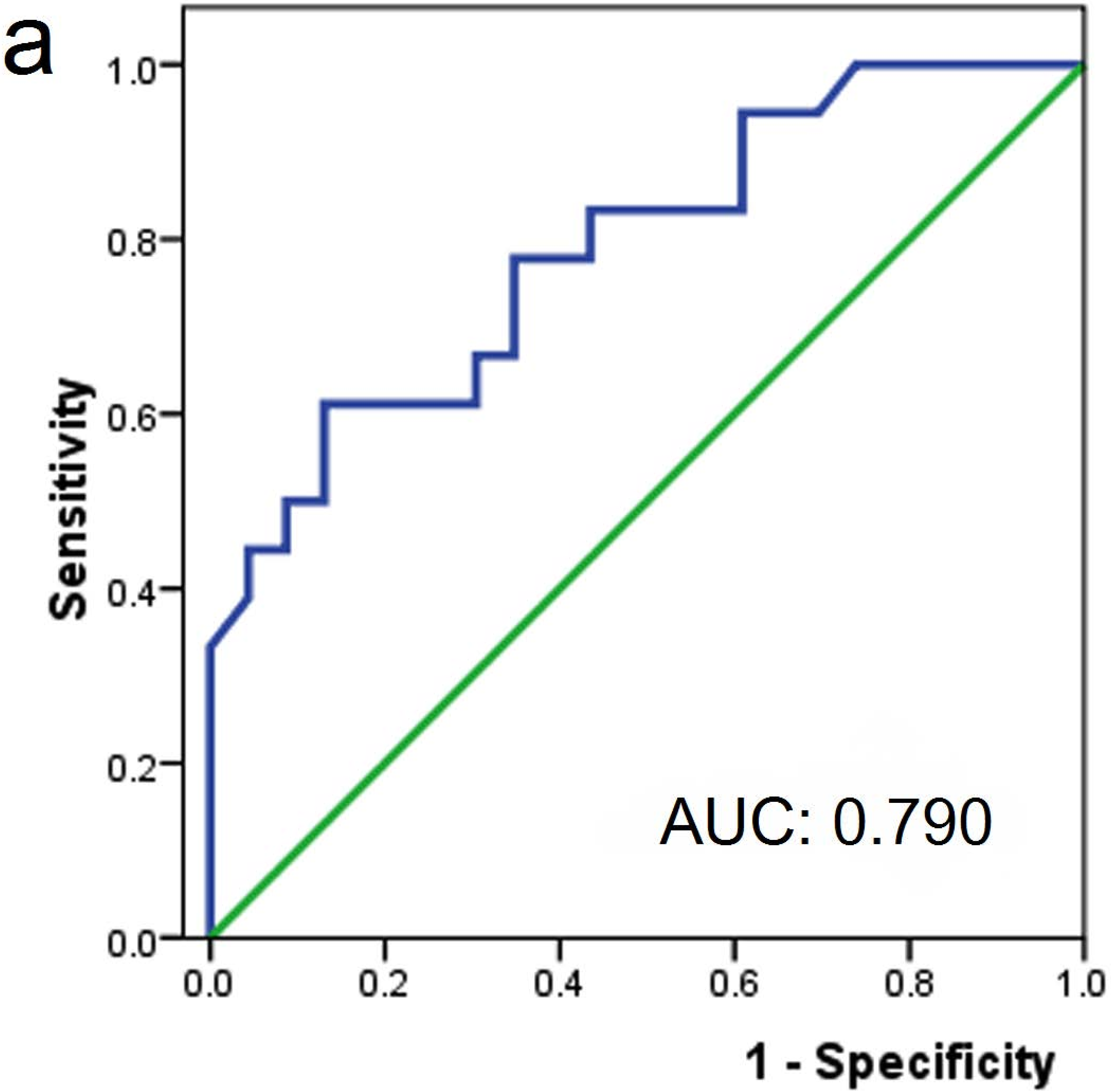
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0.2
0.0
Sensitivity
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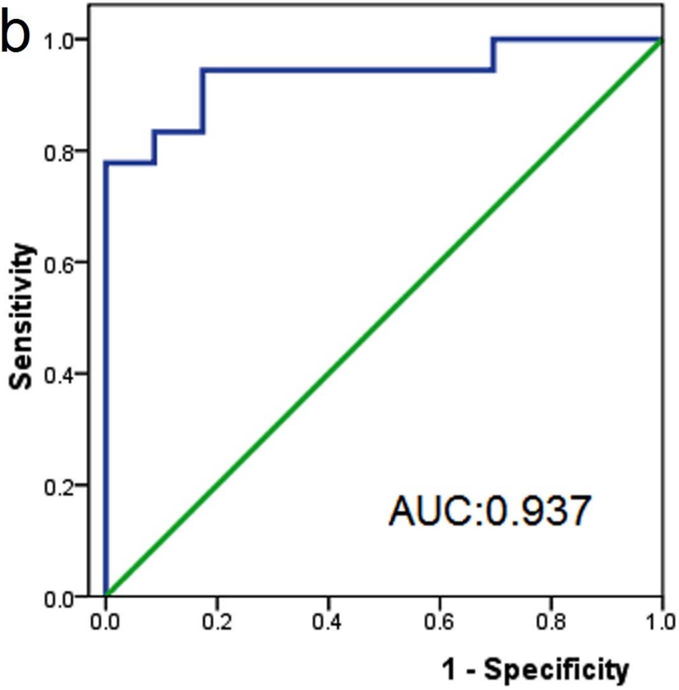
1.0
1 - Specificity
AUC: 0.790

b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0.4
0.6
0.8
1.0
AUC:0.937